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Effect of salmeterol/fluticasone propionate combination on airway hyper-responsiveness in patients with well-controlled asthma

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KEYWORDS
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Summary
Background: The hypothesis that regular treatment aimed at achieving and maintaining asthma control is accompanied by reduced airway hyper-responsiveness (AHR) was investigated.
Methods: Adult patients (PC_{20} methacholine <8 mg/ml, FEV_1% predicted $\geq 70\%$) received salmeterol/fluticasone propionate combination 50/250 μg bd (SFC250) for a 12-week run-in; those achieving well-controlled (WC) asthma were randomised to SFC250 ($n = 88$) or SFC50/500 μg bd (SFC500) ($n = 90$) for 24 weeks. AHR (PC_{20} methacholine), asthma control, lung function, symptoms, exacerbations and safety were assessed.
Results: During the 12 week run-in (SFC250), a greater than 1 doubling dose increase in PC_{20} was observed. During randomised treatment, the increase in AHR was similar, and less than 1 doubling dose, for both groups (adjusted geometric mean PC_{20} (mg/mL) at 24 weeks: SFC250: 2.796, SFC500: 2.802; $p = 0.992$). Compared with SFC250, patients receiving SFC500 had a more rapid improvement in AHR (adjusted mean ratio to baseline respectively at week 4: 1.193 vs. 1.386; week 12: 1.395 vs. 1.672; $p =$ non-significant for both) and showed a greater response to treatment in patients with a low baseline PC_{20}. Patients maintaining WC asthma were 72 (84%) and 64 (74%) in the SFC250 and SFC500 groups respectively. Both doses of SFC were well tolerated; only four exacerbations were reported, all in the SFC500 group.
Conclusion: Regular treatment with SFC resulted in continuous improvement in AHR with maintenance of asthma control in the majority of patients. SFC500 showed a trend for a more

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rapid improvement in AHR and resulted in greater improvements in patients with a lower baseline PC_{20}.

Introduction

Asthma is a chronic inflammatory disorder causing increased airway hyper-responsiveness (AHR) and episodic symptoms of wheezing, breathlessness, chest tightness and coughing.[1] Airway inflammation and AHR are frequently present when patients are asymptomatic[2–4] and there is no established relationship between asthma control, severity and level of inflammation; even patients with mild asthma show evidence of inflammation and airway remodelling.[5,6]

The aim of asthma management is to achieve and maintain asthma control by treating inflammation and relieving bronchoconstriction and symptoms.[1] Treatment guidelines recommend inhaled corticosteroids (ICS) as the most effective controller medication with the addition of a long-acting β_2-agonist (LABA) in the form of a combination therapy being advocated as the preferred add-on therapy when symptoms are not adequately controlled on ICS alone.[1,7] Despite these recommendations, most patients remain sub-optimally controlled.[8,9]

Salmeterol/fluticasone propionate combination (SFC) has been shown to significantly reduce inflammatory markers and AHR compared with fluticasone propionate alone,[10,11] which may be related to the emerging evidence that LABAs potentiate the anti-inflammatory effects of ICS.[10,12] In asthma, epithelial dysfunction may impair beta adrenoceptor function and thus contribute to AHR; and as LABAs have a beneficial impact on epithelial cell proliferation, this activity may help to protect against AHR.[13] In addition, the stepwise increase in dose in the Gaining Optimal Asthma ControL (GOAL) study showed that the majority of patients treated with SFC could achieve and maintain a composite, guideline-derived measure of asthma control.[14] The speed of response of individual control criteria was shown to vary, suggesting that assessment of one criterion may overestimate control, emphasising the importance of basing treatment changes on composite control.[15]

The current study postulated, in line with Woolcock's model,[16] that regular treatment with SFC 50/250 μg bd (SFC 250), aimed at achieving and maintaining control of asthma, would be associated with a reduction in AHR. A higher dose of SFC, 50/500 μg bd (SFC500), was included as a comparator to determine if there was any additional benefit from an increased dose.

Methods

Patients

Male or female patients, 18 years of age and older, with a history of asthma of at least six months, a PC_{20} methacholine (PC_{20})[g] <8 mg/ml and forced expiratory volume in 1 s (FEV_1) % predicted $\geq 70\%$ were recruited from 33 centres in 10 European countries. All patients were seen on an outpatients basis. Patients were required to have received FP 100 μg bd to 250 μg bd or equivalent with or without a LABA for at least 4 weeks before the run-in period. Patients who had either been hospitalized for their asthma, had a respiratory tract infection, had received systemic corticosteroids within the last 4 weeks, or were current smokers were excluded. At the end of the 12 week run-in period, patients who had their asthma assessed as well-controlled (WC), based on assessment over the last 8 weeks, were eligible for randomisation. A week of GINA[1]-derived WC asthma as defined previously, was no night-time awakenings, no exacerbations, no emergency visits, no treatment-related adverse events enforcing a change in therapy, and having 2 out of 3 of: symptom score >1[h] on ≤ 2 days, rescue β_2-agonist use on ≤ 2 days and ≤ 4 occasions per week, and daily morning peak expiratory flow (PEF) $\geq 80\%$ predicted.[14]

Study design

This multi-centre, stratified, double-blind, randomised, parallel-group study was conducted in 34 centres in 10 European countries. Following a 12 week open-label, run-in period, during which all patients received SFC250, those assessed as having WC asthma, were randomised to either continue treatment with SFC250 or to receive SFC500, for 24 weeks. Randomisation was stratified according to previous ICS dose (ICS dose FP 100 μg bd or equivalent or FP 250 μg bd or equivalent) and AHR at randomisation visit ($PC_{20} \geq 2$ mg/ml or < 2 mg/ml). Both treatments were supplied by GlaxoSmithKline (GSK) in identical Diskus devices to blind treatment. Patients were assessed at Weeks 4, 12 and 24 of treatment. The study was approved by a national, regional, or investigational centre ethics committee or institutional review board according to local laws and regulations. Written informed consent was obtained from each patient prior to any study-specific procedures.

Efficacy assessments

The primary endpoint was mean change in PC_{20} following 24 weeks of treatment. Methacholine challenges were performed by the standardised 2 min tidal breathing method,[17] using Provocholine (Methapharm Inc, Brantford, Canada). Response was expressed as the provocative concentration causing a 20% fall in post-saline FEV_1 (PC_{20}), calculated by linear interpolation of two adjacent data points. Patients who completed the challenge to the highest dose of 32 mg/ml without achieving a 20% fall, were included in the analysis as having a PC_{20} of 64 mg/ml. Methacholine challenge was not performed if baseline FEV_1 was $<70\%$

[g] Provocative concentration of methacholine causing forced expiratory volume in 1 s (FEV^1) to fall by 20% from post-saline baseline.

[h] Symptom score: 1 was defined as 'symptoms for one short period during the day'; overall scale: 0 (none) to 5 (severe).

predicted or the visit was within 4 weeks after the end of a short course of oral corticosteroids. An increase in PC_{20} of $\geq$1 doubling dose is considered a clinically relevant improvement.

Secondary endpoints were asthma control, lung function PEF, FEV_1 and forced vital capacity [FVC]), asthma symptoms, rescue medication use and exacerbations.

The proportion of patients maintaining WC asthma (see definition above) or achieving Totally Controlled (TC) asthma was assessed over the last 8 weeks of treatment. A week of TC asthma was defined as no symptoms, no rescue medication use, no night-time awakenings, no exacerbations, no emergency visits, no treatment-related adverse events enforcing a change in therapy and daily morning PEF $\geq$80% predicted.[14]

Spirometry was performed according to European Community for Coal and Steel (ECCS) recommendations;[18] patients were asked to refrain from using short-acting bronchodilators for at least 6 h and study medication for 36 h prior to each visit. The highest of three PEF measurements were recorded each morning prior to taking any study or rescue medication. A score for asthma symptoms over the last 24 h was recorded each morning (scale from 0 representing 'no symptoms' to 5 representing 'symptoms so severe that patient could not go to work or perform normal activities').

Asthma exacerbations were monitored throughout the study and defined as a deterioration of asthma requiring administration of oral corticosteroids and/or deterioration in asthma requiring emergency room visit and/or admission to hospital.

Safety assessments

Safety was assessed by the monitoring of adverse events. Such data were collected throughout the study including serious adverse events and any events which, in the opinion of the clinician, were considered related to treatment.

Statistical analyses

Based on the number of patients required to detect a single doubling dose difference in PC_{20}, with 90% power, a sample size of 60 evaluable patients per group was estimated. All analyses were based on the Intention-to-Treat population and significance testing used a two-sided test conducted at the 0.05 significance level. Mean change from baseline in PC_{20} at Week 24 was compared using an analysis of covariance (ANCOVA) model, allowing for effects due to treatment, baseline (randomisation) PC_{20}, pre-study ICS dose, age, sex and country amalgamation. The proportion of patients with WC and TC asthma were compared using separate logistic regression models, and the change from baseline in pre-bronchodilator FEV_1 and FVC were analysed using ANCOVA. All efficacy data for PEF, asthma symptoms and rescue medication use, and all safety data were summarised. Tests for two-factor interactions between treatment and pre-study ICS dose, age, baseline PC_{20}, country amalgamation and sex were performed (pre-defined significance level of 0.10).

Results

Patient characteristics

A total of 369 patients were screened for entry to the study of which 178 were randomised to double-blind treatment, 88 to SFC 250 and 90 to SFC500 (Fig. 1). The two groups were well matched both demographically and for baseline lung function and symptom scores. Values were consistent with the randomisation of patients with WC asthma (Table 1). Baseline (end of run-in) values for PEF and FEV_1 were slightly higher in the SFC500 group, as was baseline mean PC_{20} (SFC500: 1.77 mg/mL; SFC 250: 1.48 mg/mL) (Table 1)

Efficacy assessments

Run-in

During the 12 week run-in period (treatment SFC250), there was a greater than 1 doubling dose increase in PC_{20} in both groups: SFC250 increase from 0.64 mg/mL to 1.48 mg/mL; SFC500 increase from 0.67 mg/mL to 1.77 mg/mL (Table 1, Fig. 2). Mean PEF and FEV_1 also increased during the run-in period (Table 1).

Randomised treatment period

PC_{20} methacholine

During the 24 week randomised treatment period PC_{20} increased in both treatment groups with a less than 1 doubling dose increase observed in both groups (end of run-in baseline to week 24 geometric mean: 1.62—2.80 mg/mL in the SFC250 group and 1.83—2.80 mg/mL in the SFC500 group, $p = 0.992$) (Table 2, Fig. 2). However over the entire SFC treatment period (including run-in), a greater than two-fold improvement in AHR was observed in both groups. At the randomisation visit (end of run-in) 11 (13%) patients in the SFC250 group and 15 (17%) patients in the SFC500 group demonstrated AHR within the normal range (>8 mg/mL). At subsequent visits, the number of patients with a PC_{20}>8 mg/mL for SFC250 and SFC500 respectively: Week 4: 15 (17%) and 19 (21%); Week 12: 18 (20%) and 23 (26%); Week 24: 23 (26%) and 20 (22%).

For both groups, a faster improvement in PC_{20} was observed in the first 12 weeks of randomised treatment followed by a smaller improvement from week 12 onwards (Fig. 2). Compared with SFC250, a more rapid improvement was observed with SFC500, evidenced by a greater PC_{20} adjusted geometric mean ratio to baseline at weeks 4 and 12 of treatment, although these differences were not statistically significant (Table 2).

A significant interaction with treatment and baseline PC_{20} was observed ($p = 0.047$), the model estimating that patients who started with a lower baseline PC_{20} had a better treatment response to the higher dose of SFC than those who started with a higher baseline PC_{20} (Fig. 3).

Secondary efficacy assessments

The results for secondary efficacy assessments are summarised in Table 3. Over the last eight weeks of randomised treatment, the majority of patients in both groups maintained their WC asthma status with no significant difference

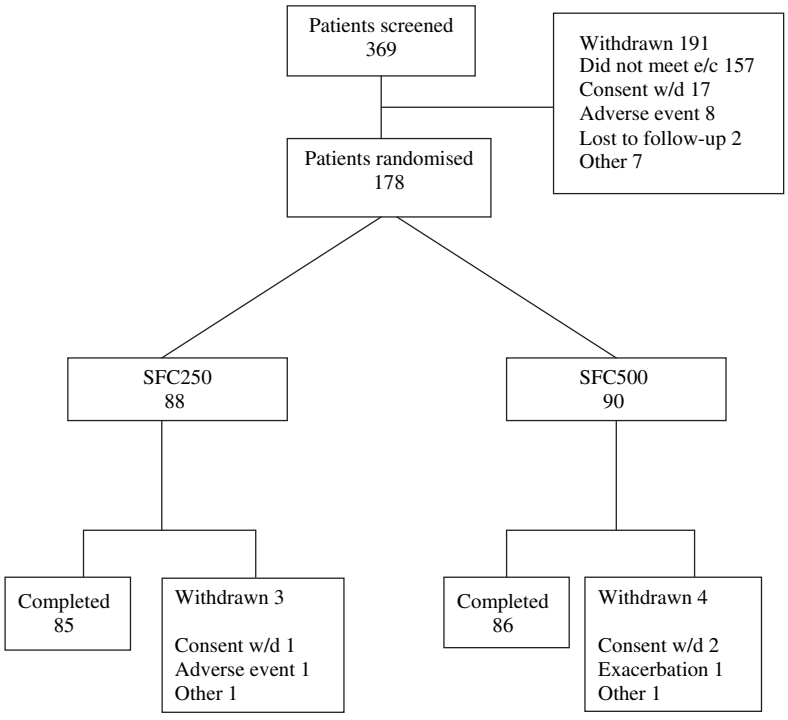

Figure 1 Subject flow through the study. SFC250 = salmeterol/fluticasone propionate combination 50/250 μg bd, SFC500 = salmeterol/fluticasone propionate combination 50/500 μg bd, w/d = withdrawn, e/c = entry criteria.

between groups in the odds of maintaining WC asthma vs losing WC status (Odds Ratio SFC500 to SFC250: 0.58; 95% CL: 0.23, 1.43; $p = 0.235$). Approximately a quarter of patients in each group achieved Totally Controlled asthma (meaning no clinical symptoms) over the last 8 weeks of treatment.

Patients assessed as not WC over the last 8 weeks of treatment showed less improvement in PC_{20} over 24 weeks than those assessed as having WC or TC asthma. However improvement in the WC patients was greater than those assessed as TC: PC_{20} geometric mean ratio [CV] of Week 24 to baseline values [mg/mL] for the whole study population (i.e. not split by treatment group): No WC asthma: 1.26 [209.82]; WC asthma: 1.75 [243.35]; TC asthma: 1.53 [276.89] (Fig. 4).

There was a small difference between treatment groups in change in FEV_1 over treatment in favour of the SFC500 group (treatment difference 80 mL, $p = 0.048$) (Table 3).

Table 1 Demography and baseline characteristics.

Parameter	SFC250 ($N = 88$)	SFC500 ($N = 90$)
Mean Age (range) (years)	44.4 (18–71)	42.1 (18–73)
Male Sex, n (%)	34 (39)	48 (53)
PC_{20}[a] (mg/mL),		
Geometric mean (CV)		
Start of run-in	0.64 (303.70)	0.67 (336.83)
End of run-in	1.48 (575.10)	1.77 (574.33)
Lung function, mean (SD)		
Start of run-in: PEF (L/min)	459.0 (95.7)	472.0 (96.8)
FEV_1 (L)	2.96 (0.88)	3.10 (0.78)
% predicted FEV_1	93.4 (14.9)	89.7 (15.1)
End of run-in: PEF (L/min)	473.5 (100.07)	485.2 (93.69)
FEV_1 (L)	3.00 (0.88)	3.17 (0.78)
% predicted FEV_1	94.9 (15.4)	91.8 (14.0)
Mean Symptoms(SD) during run-in		
24 h symptom score	0.34 (0.36)	0.36 (0.39)
Night-time awakenings	0.03 (0.19)	0.04 (0.23)

[a] Provocative concentration of methacholine causing forced expiratory volume in 1 s (FEV_1) to fall by 20% from post-saline baseline; SFC250 = salmeterol/fluticasone propionate combination 50/250 μg bd, SFC500 = salmeterol/fluticasone propionate combination 50/500 μg bd; SD = standard deviation; CV = coefficient of Variation.

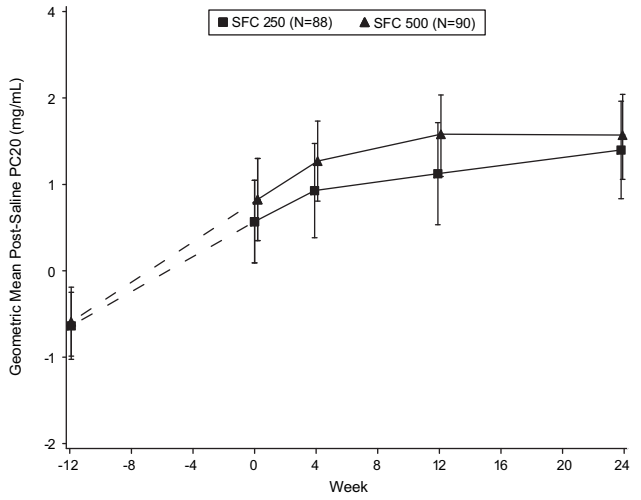

Figure 2 PC_{20} methacholine over time. —■— SFC50/250 run-in, then —■— SFC50/250 randomised treatment —▲— SFC50/250 run-in, then —▲— SFC50/500 randomised treatment. SFC 50/250 = salmeterol/fluticasone propionate combination 50/250 μg bd, SFC50/500 = salmeterol/fluticasone propionate combination 50/500 μg bd. *Y*-axis is on the log scale. Difference between treatments non-significant.

Other minor changes in lung function indices and asthma symptoms were observed and were similar in both treatment groups.

During treatment very few exacerbations were reported. No patients in the SFC250 group had an exacerbation and four patients in SFC500 group each had one exacerbation. Of these, none resulted in hospitalization and three required treatment with oral corticosteroids.

Safety assessments

Overall, both doses of SFC were well tolerated with a similar proportion of patients reporting an adverse event in each group: 39 (44%) patients in the SFC250 group and 36 (40%) patients in the SFC500 group. Nasopharyngitis was the most commonly reported event in both groups (16% and 13% respectively). The incidence of serious adverse events and drug-related events was very low for both treatment groups.

Discussion

This study showed that, in adult patients with well-controlled asthma, treatment with SFC250 or SFC500 for 24 weeks resulted in a continuous improvement in AHR together with maintenance of asthma control in the majority of patients. These results are important as they support the view that a strategy based on regular and continued treatment with SFC, during which control is achieved and maintained, can contribute to a potential change in asthma severity, making a valid contribution to the concept that sustained treatment may result in sustained improvement of disease characteristics.

These results reinforce the importance of the time-course for changes in AHR and show that this is the case even for patients who appear to have clinically controlled asthma. Although during randomised treatment the increase in PC_{20} was less than 1 doubling dose, when the run-in is considered, a greater than two-fold improvement in PC_{20} was demonstrated over 9 months. In a study evaluating the effect of high dose FP (750 μg bd), Ward et al[4] also showed that the time-course for improvement in spirometry, inflammation, airway remodelling and AHR was

Table 2 PC_{20} Methacholine.

PC_{20} Methacholine[a] (mg/mL)	SFC250 (*N* = 88)		SFC500 (*N* = 90)
Screening, geometric mean (CV)	0.64 (303.70)		0.67 (336.84)
Baseline,[b] geometric mean (CV)	1.62 (483.53)		1.83 (619.14)
Week 4, *n*	84		83
Mean[c] ratio to baseline (CV)	1.19 (12.93)		1.39 (13.01)
SFC500/SFC 250 ratio (SE)		1.16 (0.22)	
95% CI		0.855, 1.578	
p-Value[c]		0.335	
Week 12, *n*	82; 1.40 (14.68)		86 1.67 (14.31)
Mean[c] ratio to baseline (CV)			
SFC500/SFC 250 ratio (SE)		1.20 (0.25)	
95% CI		0.852, 1.687	
p-value[d]		0.295	
Week 24, *n*	81; 1.62 (15.55)		82 1.63 (15.45)
Mean[c] ratio to baseline (CV)			
SFC500/SFC 250 ratio (SE)		1.00 (0.27)	
95% CI		0.696, 1.442	
p-value[d]		0.992	

SFC250 = salmeterol/fluticasone propionate combination 50/250 μg bd, SFC500 = salmeterol/fluticasone propionate combination 50/500 μg bd; CV = coefficient of variation; SE = standard error.

[a] Provocative concentration of methacholine causing forced expiratory volume in 1 s (FEV_1) to fall by 20% from post-saline baseline.

[b] Includes only patients who also had a week 24 PC_{20} measurement, accounting for difference from baseline shown in Table 1.

[c] Adjusted geometric mean.

[d] statistical comparison used ANCOVA model of Log_2 (PC_{20} Ratio to Baseline), adjusted for baseline, $Log_2(PC_{20})$, pre-study medication ICS dose, age, sex and country amalgamation.

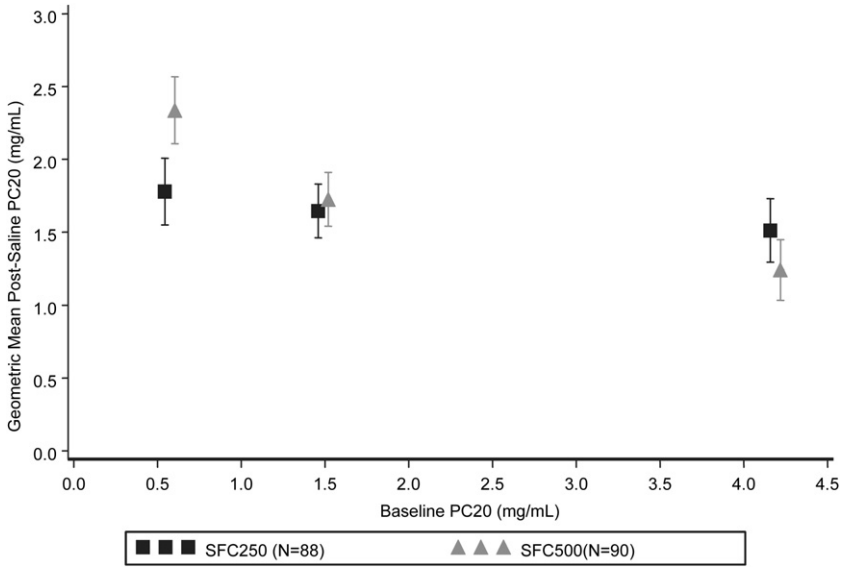

Figure 3 PC_{20} methacholine at week 24 by baseline PC_{20}. ■■■ = salmeterol/fluticasone propionate combination 50/250 μg bd; ▲▲▲ = salmeterol/fluticasone propionate combination 50/500 μg bd. *Y*-axis is on the log scale.

discordant, concluding that prolonged treatment is required for maximal benefit in airway remodelling and AHR. The importance of monitoring AHR in the long-term management of asthma was demonstrated with a treatment strategy aimed at decreasing AHR in addition to the recommendations in existing guidelines, resulting in better outcomes for exacerbation rates (a strong criterion for asthma control), lung function and markers of

Table 3 Secondary efficacy assessments.

	SFC250 ($N = 88$)		SFC500 ($N = 90$)
Asthma Control, weeks 17–24, *n*	86		86
Maintained WC asthma, *n* (%)	72 (84)		64 (74)
Achieved TC asthma, *n* (%)	24 (28)		22 (26)
Unevaluable	4 (5)		6 (7)
Pre-bronchodilator FEV_1 (L)	−0.04(0.03)		0.04 (0.03)
Mean change (SE)[a]			
Treatment difference (95% CI)		0.08 (0.00, 0.16)	
p-Value[b]		0.048	
Pre-bronchodilator FVC (L)	−0.05(0.036)		−0.02(0.036)
Mean change (SE)[a]			
Treatment difference (95% CI)		0.03 (−0.07, 0.13)	
p-value[b]		0.526	
Mean Morning PEF (L/min) (SD)			
Baseline[c]	469.9 (95.9)		484.8 (95.0)
Weeks 17–24	478.5 (97.1)		491.8 (93.6)
Mean 24-h Asthma symptom score (SD)			
Baseline[c]	0.34 (0.36)		0.36 (0.39)
Weeks 17–24	0.23 (0.35)		0.30 (0.52)
Mean Night-time awakenings (SD)			
Baseline[c]	0.03 (0.19)		0.04 (0.23)
Weeks 17–24	0.04 (0.20)		0.03 (0.20)
Mean Median Rescue Medication Use (SD)			
Baseline[c]	0.05 (0.26)		0.07 (0.41)
Weeks 17–24	0.08 (0.28)		0.08 (0.49)

[a] Week 24, adjusted mean change from baseline.
[b] Statistical comparison used ANCOVA model of change from baseline, adjusted for baseline PC_{20} pre-study medication ICS dose, age, sex and country amalgamation.
[c] Baseline over weeks −8 to −1; WC = well-controlled; TC = totally controlled; FEV_1 = forced expiratory volume in 1 s; SFC250 = salmeterol/fluticasone propionate combination 50/250 μg bd, SFC500 = salmeterol/fluticasone propionate combination 50/500 μg bd; FVC = forced vital capacity; PEF = peak expiratory flow; SD = standard deviation.

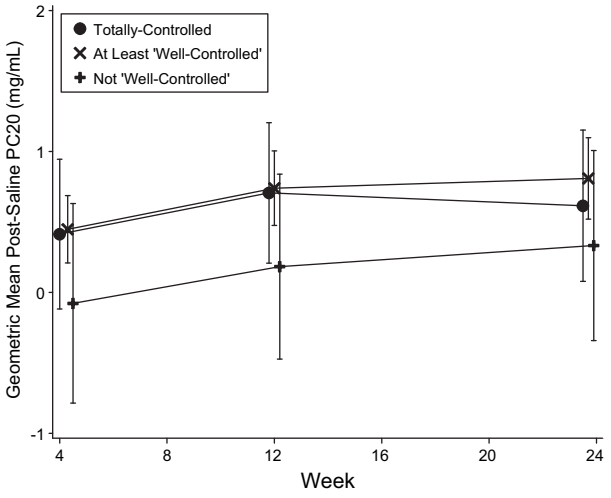

Figure 4 PC_{20} methacholine ratio to baseline values by control status: Not Well-Controlled, $N = 26$; At Least Well-Controlled includes Well-Controlled and Totally Controlled patients, $N = 135$; Totally Controlled, $N = 45$. *Y*-axis is on the log scale.

inflammation compared with a strategy based on guidelines alone.[19] However, Koenig et al. showed that, for most patients, improvement in AHR was maintained when a treatment strategy aimed at controlling clinical parameters alone was used.[20] The CATO study group found, in a group of moderate asthmatic children, that a treatment strategy guided by AHR showed no benefits in terms of symptom-free days but produced a better long-term outcome on FEV_1, particularly in a sub-group exhibiting low symptom scores but with associated AHR.[21] Therefore, current treatment guidelines, based on symptoms and lung function alone, could result in anti-inflammatory treatment being stepped down too early in patients with persisting AHR in the absence of symptoms. A recent American Thoracic Society/European Respiratory Society Task Force identified the need to consider the relationship between control, severity and phenotypes in the context of treating asthma and assessing future risk. The authors suggested that characterizing populations by their phenotype can provide important additional information to the assessment of current clinical control,[22] and the findings of our study are consistent with this view.

The results of our study concur with the findings of a one year study by Lundback et al. showing that regular treatment with SFC resulted in significantly fewer exacerbations and greater improvements in AHR compared with treatment with monotherapy with either FP or salmeterol.[11] A subsequent, two year open extension showed that clinical control could be maintained over three years following physician-driven treatment changes: 73% patients were treated with SFC to maintain control compared with FP alone (21%) or salmeterol alone (5%). AHR continued to improve over the three years.[23] The results are also consistent with the GOAL study, demonstrating that regular treatment with SFC results in achieving and maintaining clinical control.[14] In our study, the benefits on asthma control appear to be related more to the regular use of treatment rather than the dose used. The statistically significant difference in FEV_1 in favour of the high dose group was not considered clinically significant. No significant benefit of the increased dose was observed in this study for PC_{20} which concurs with the findings of Reddel et al. who demonstrated, in patients with poorly controlled asthma, that a daily dose of 1600 μg budesonide resulted in optimal control in most patients with no additional benefit derived from a starting dose of 3200 μg[24] However, in our study an interesting interaction between treatment and baseline PC_{20} was investigated and indicated that patients with a lower baseline PC_{20} showed a better response to the higher dose of SFC. In addition, the improvements in the SFC500 group appeared to be achieved more rapidly, as evidenced by a higher, albeit non-significant, PC_{20} at weeks 4 and 12 of treatment. A more rapid improvement in AHR was also observed by the Reddel group during the first 8 weeks of treatment with budesonide 3200 μg daily compared with 1600 μg daily.[24] Therefore a sub-group of patients with a low PC_{20} may benefit the most from a higher starting dose of SFC.

AHR is a marker of the natural history or severity of the disease rather than a criteria for control (long term vs. short term).[22] The importance of measuring bronchial responsiveness was also demonstrated by the SAPALDIA group who showed that, in formerly asymptomatic patients, AHR was a risk factor for accelerated decline in FEV_1 and development of asthma.[25] Similarly, Limb et al. demonstrated that factors in childhood that could identify individuals at risk for irreversible lung function deficits in adulthood included abnormal spirometry, low PC_{20} and duration of asthma.[26]

The number of exacerbations reported was higher in the SFC500 group compared with SFC 250 (four vs. none respectively), although a treatment duration of 24 weeks may be considered too short to gather meaningful data on exacerbations. However, this rate is very low and consistent with the low rates of exacerbations reported in other studies with SFC.[14,27] The overall incidence of serious adverse events, drug-related events and withdrawals due to events was very low, and no safety issues or significant differences between treatments were identified.

In conclusion, this study showed that regular treatment with SFC resulted in continuous improvement in AHR with maintenance of asthma control in the majority of patients. SFC500 showed a trend for a more rapid improvement in AHR and resulted in greater improvements in patients with a lower baseline PC_{20}. Notably, changes in AHR as a marker of disease modification takes longer than clinical control, and studies are needed to identify the appropriate time to initiate step-down therapy.

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All authors were involved in the interpretation of the results and the decision to submit the paper for publication.

Conflict of interest statement

This analysis was funded by GlaxoSmithKline (GSK). GJ was involved in the design of the study. PC has received financial support from GSK, AstraZeneca, Chiesi, Novarti, Centocor, Schering Plough and Actelion for lecturing, consultancies and serving on advisory boards. RS and his institution have received financial support from GSK, Boehringer Ingelheim, Covance and Chiesi for performing research. RS has received financial support from GSK, AstraZeneca, Merck, Sharp & Dohme (MSD) and Schering Plough, for lecturing, consultancies and serving on advisory boards. GJ has received financial support from GSK, AstraZeneca, Boehringer Ingelheim, Novartis, UCB, MSD, Almirall, and Nycomed for sponsorship, research, consultancies and advisory boards. P Bloemen and L Adamek are employees of GSK.

Ethical approval

The study was conducted in accordance with "good clinical practice", all applicable subject privacy requirements, and, the guiding principles of the Declaration of Helsinki.

The study was approved by a national, regional, or investigational centre ethics committee or institutional review board according to local laws and regulations. Written informed consent was obtained from each patient prior to any study-specific procedures.

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